

## PRESS RELEASE

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### **NUS scientists' discovery sheds light on lung cancers' resistance to treatment**

*Singapore, 29 June 2018* — Cells use nutrients such as glucose, amino acids and fat (lipids) to produce the energy to support the essential processes that keep them alive and functioning. Cancer cells, those ultimate survivors, have figured out a way to tweak their own metabolism to increase the supply of energy, allowing them to multiply uncontrollably. These altered metabolic pathways can serve as targets for new cancer therapies, a team of researchers at the National University of Singapore (NUS) has found.

Led by Dr Azhar Ali, Senior Research Scientist at Cancer Science Institute of Singapore (CSI), NUS, the team of researchers at CSI and Beth Israel Deaconess Medical Center in the United States (US), has discovered that a key enzyme in lipid metabolism controls the response to a class of targeted drugs called tyrosine kinase inhibitors (TKIs) in lung cancer.

Lung cancer is the most common cancer in the world and the top cause of cancer deaths, accounting for one in five deaths from cancer.<sup>1</sup> A large majority of lung cancers (85%) are known as non-small cell lung cancers (NSCLC). A significant proportion of NSCLC patients (10%-15% in Europe and the US, and more than 40% in Asia) have gene alterations (or mutations) in the epidermal growth factor receptor (EGFR) gene.<sup>2</sup>

Currently, the most effective treatment for this type of NSCLC are TKIs that specifically target the altered EGFR, with an overall survival of two to four years.<sup>3-5</sup> However, over time, resistance to TKIs develops. At that point, patients have very limited treatment options and a very poor prognosis.

Understanding how this inevitable resistance to TKIs develops is crucial to tackling the problem. Several different mechanisms for TKI resistance in this type of lung cancer have already been described. Taking this understanding further, Dr Azhar, Dr Chin Tan Min, Specialist in Medical Oncology at Raffles Cancer Centre, Professor Daniel Tenen, Director of CSI, and colleagues discovered a completely new mechanism involving fatty acid synthase (FASN), a key enzyme in lipid synthesis that facilitates the production of the saturated fatty acid palmitate.<sup>6</sup> When palmitate modifies mutated EGFR in the cancer cells, it affects the way these tumor cells behave, making them resistant to the effects of TKIs.

Orlistat is a weight loss drug that blocks FASN, thus preventing the production of palmitate. In resistant cells, without palmitate, EGFR can no longer be modified by palmitate and is degraded instead. Treatment with Orlistat stunted the growth of EGFR-mutated NSCLC cells in cell culture systems and preclinical models. These findings provide strong evidence of the importance of FASN in survival and growth of this common type of lung cancer.

The next step is to target FASN using a modified version of Orlistat, which is poorly distributed throughout the body when given orally. A more effective therapy that blocks FASN will serve as a valuable treatment option for NSCLC patients with EGFR mutations who have developed resistance to TKI drugs.

"Identifying molecular targets that are responsible for the development of resistance to chemotherapy has important implications for treatment. Drugs that interfere with fatty acid synthesis may thus be useful in treating these lung tumours that are driven by FASN and resistant to TKI drugs," said Dr Azhar.

## References

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For media enquiries, please contact:

WANG Simin  
Assistant Manager, Communications  
Yong Loo Lin School of Medicine  
National University of Singapore  
DID: +65 6772 7804  
Mobile: +65 9625 3710  
Email: [wangsimin@nus.edu.sg](mailto:wangsimin@nus.edu.sg)

Janice TAY  
Senior Executive, Outreach  
Cancer Science Institute of Singapore  
National University of Singapore  
DID: +65 6516 7980  
Email: [csitsrj@nus.edu.sg](mailto:csitsrj@nus.edu.sg)

## **About the National University of Singapore (NUS)**

A leading global university centred in Asia, the National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education and research, with a focus on Asian perspectives and expertise.

NUS has 17 Faculties and Schools across three campuses. Its transformative education includes a broad-based curriculum underscored by multidisciplinary courses and cross-faculty enrichment. Over 38,000 students from 100 countries enrich the community with their diverse social and cultural perspectives. NUS also strives to create a supportive and innovative environment to promote creative enterprise within its community.

NUS takes an integrated and multidisciplinary approach to research, working with partners from industry, government and academia, to address crucial and complex issues relevant to Asia and the world. Researchers in NUS' Faculties and Schools, 30 university-level research institutes and centres, and Research Centres of Excellence cover a wide range of themes including: energy, environmental and urban sustainability; treatment and prevention of diseases common among Asians; active ageing; advanced materials; risk management and resilience of financial systems. The University's latest research focus is to use data science, operations research and cybersecurity to support Singapore's Smart Nation initiative.

For more information on NUS, please visit [www.nus.edu.sg](http://www.nus.edu.sg).

## **About Cancer Science Institute of Singapore (CSI)**

CSI Singapore is a state-of-the-art university research institute affiliated with, and hosted at the National University of Singapore. It was established in 2008, with a "Research Center of Excellence" grant, one of only five in Singapore, by the National Research Foundation and the Ministry of Education. Professor Daniel G. Tenen, MD, a leader in the field of transcriptional regulation, hematopoiesis, and cancer, was named its founding director.

The institute is an anchor for research expertise in three broad programs; Cancer Biology & Stem Cells, Experimental Therapeutics, and the RNA Biology Center; these programs form expansive platforms for CSI Singapore's focus on key cancer disease cancers in gastric, liver, lung and leukemia which are endemic in Asian populations. CSI Singapore aims to position Singapore as a global-leader in the field of Biomedical Sciences. Its mission: to conduct a multifaceted and coordinated approach to cancer research, extending from basic cancer studies all the way to experimental therapeutics and in so doing improve cancer treatment.

For more information on CSI, please visit <https://www.csi.nus.edu.sg/ws/>